CONTROL ID: 2671102
SUBMISSION ROLE: Abstract Submission

AUTHORS

AUTHORS (LAST NAME, FIRST NAME): Wosikowski, Katja[1]; van Hoven, Inge[3]; Puranen, Jooseppi[2]; de Groef, Lies[3]; Haapaniemi, Anne Mari[2]; Sergeys, Jurgen[3]; Kaja, Simon[2]; Kalesnykas, Giedrius[2]; Moons, Lieve K.[3]; Janicot, Michel[1]

INSTITUTIONS (ALL):
1. Preclinical Research and Development, Isarna Therapeutics, Munich, Germany.
2. Experimentica, Kuopio, Finland.
3. Biology Department, Zoological Institute, KU Leuven, Leuven, Belgium.

Commercial Relationships Disclosure (Abstract): Katja Wosikowski: Commercial Relationship(s);Isarna Therapeutics:Code E (Employment) | Inge van Hoven: Commercial Relationship(s);Isarna Therapeutics:Code F (Financial Support) | Jooseppi Puranen: Commercial Relationship(s);Experimentica:Code E (Employment) | Lies de Groef: Commercial Relationship(s);Isarna Therapeutics:Code F (Financial Support) | Anne Mari Haapaniemi: Commercial Relationship(s);Experimentica:Code E (Employment) | Jurgen Sergeys: Commercial Relationship(s);Isarna Therapeutics:Code E (Employment) | Simon Kaja: Commercial Relationship(s);Experimentica:Code C (Consultant) | Giedrius Kalesnykas: Commercial Relationship(s);Experimentica:Code E (Employment) | Lieve Moons: Commercial Relationship(s);Isarna-Therapeutics:Code F (Financial Support) | Michel Janicot: Commercial Relationship(s);Isarna-Therapeutics:Code C (Consultant)

Study Group: (none)

ABSTRACT

TITLE: Targeting Transforming Growth Factor beta 2 (TGF-β2) mRNA with ISTH0036 as Novel Therapeutic Intervention in Neovascular Ocular Disease

ABSTRACT BODY:

Purpose: Although anti-VEGF therapeutics represent a significant step forward in treating neovascular eye diseases, insufficient response to anti-VEGF-treatments represents a significant clinical problem. Therefore, novel therapies with alternative molecular mechanisms of action are desirable. We recently reported potent activity of ISTH0036, a LNA-modified antisense oligonucleotide specifically targeting the sequence of TGF-β2 mRNA, in a murine glaucoma filtration surgery model. The aim of the present studies was to evaluate the therapeutic potential of ISTH0036 in a murine model of laser-induced choroidal neovascularization (CNV).

Methods: Effect of ISTH0036 on TGF-β2 mRNA expression and cell migration was explored on murine astrocytes to ensure target engagement and pharmacological effect in these cells. The posterior eye tissue distribution was determined following intravitreal (IVT) injection of DIG-labeled ISTH0036. Subsequently, the effect of the drug was studied in a murine CNV model by performing 3 laser-induced burns on the Bruch's membrane of the eyes (n= 5-9 mice/group). IVT injections of test items were performed directly after laser treatment. Experimental outcomes included inflammation (CD45 staining, on day 5), presence of CNV pathology (FA and OCT, on days 5-14), angiogenesis (FITC-dextran staining, on day 14), and fibrotic processes (collagen I deposition, on day 28).

Results: ISTH0036 showed potent downregulation of target mRNA and inhibition of migration of murine astrocytes in cell based assays. ISTH0036 was detectable in most of the tested posterior eye tissues; including sclera, retina, choroid and ciliary body. In the murine CNV model, ISTH0036 was shown to significantly reduce the process of angiogenesis in a dose-and sequence-dependent manner. Beneficial inhibitory effect of ISTH0036 on the progression of CNV pathology and vascular leakage was demonstrated. In addition, and in contrast to existing anti-VEGF treatments, deposition of collagen was significantly reduced with ISTH0036.

Conclusions: Our results confirm that targeting TGF-β2 in CNV may represent an attractive modality for the effective treatment of neovascular ocular diseases such as wet AMD and diabetic retinopathy. Demonstrated potent inhibitory effects on vascular leakage, angiogenesis and fibrosis support further clinical development of ISTH0036 in these

relevant indications.
(No Image Selected)

DETAILS

PRESENTATION TYPE: #1 Poster, #2 Paper
CURRENT REVIEWING CODE: 1360 AMD: new drugs, delivery systems, and mechanisms of action - PH
CURRENT SECTION: Physiology/Pharmacology
Clinical Trial Registration (Abstract): No
Other Registry Site (Abstract): (none)
Registration Number (Abstract): (none)
Date Trial was Registered (MM/DD/YYYY) (Abstract): (none)
Date Trial Began (MM/DD/YYYY) (Abstract): (none)
Grant Support (Abstract): No
Support Detail (Abstract): None

TRAVEL GRANTS and AWARDS APPLICATIONS

AWARDS:

AFFIRMATIONS

Affirmations: Affirmation that submission of this abstract has been approved by the Principal Investigator.
Affirmations: Affirmation that abstract data/conclusions have not been published; not redundant with other submissions from same investigators.
Affirmations: Affirmation to reveal essential structure, novel compound elements, or identify new gene compounds.
Affirmations: Affirmation of copyright transfer from each author to ARVO, or certification of public domain abstract.
Affirmations: Affirmation of compliance with ARVO’s Statement for Use of Animals.
Affirmations: Affirmation of compliance with ARVO’s Statement for Use of Human Subjects and/or Declaration of Helsinki.
Affirmations: Affirmation of compliance with ARVO policy on registering clinical trials.
Affirmations: Affirmation to pay Annual Meeting’s full registration fee.
Affirmations: Affirmation to present same work as abstract submission.